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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/625,245 | 07/22/2003 | Shuichi Mizuno | 3831.08 | 9296 |

23308 7590 07/01/2008

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| EXAMINER | |
|---|---|
| NAFF, DAVID M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1657 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 07/01/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/625,245 | MIZUNO ET AL. | |
| | Examiner | Art Unit | |
| | David M. Naff | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *64-67,69-71,73-75 and 83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-67, 69-71, 73-75 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

An amendment of 3/6/08 amended claims 64, 66, 67, 69-71, 73 and 74, added new claims 75 and 83, and canceled claims 63, 68, 72 and 76-82.

Claim 75 is new since previous claims in the case did not contain a claim numbered 75.

Claims examined on the merits are 64-67, 69-71, 73-75 and 83, which are all claims in the application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not found in the specification for a construct “consisting essentially of” as recited in line 1 of claim 83. The specification fails to recite “consisting essentially of”.

In line 8 of claim 83, the specification fails to support or recite “repeatedly applying” a cyclic hydrostatic pressure followed by a constant atmospheric pressure”.

In line 12 of claim 83, the specification fails to recite “extracellular matrix macromolecules Type II collagen”, and support for this term is not found. While the specification discloses increased production of Type II collagen due to activation, no disclosure is found of the Type II collagen being extracellular matrix macromolecules.

In line 12 of claim 83, the abbreviation "S-GAG" should be in parenthesis and preceded by the full name. Thereafter, only the abbreviation may be used.

In lines 18-19 of claim 83, the specification fails to disclose Type II collagen and S-GAG being produced by synthesized extracellular matrix. While the specification discloses increased production of Type II collagen and S-GAG by dividing and multiplying chondrocytes, disclosure is not found of the extacellular matrix producing Type II collagen and S-GAG.

In lines 20-22 of claim 83, the specification fails to disclose that mature chondrocytes are unable to produce extracellular matrix macromolecules. The specification discloses that mature cartilage tissue contains metabolically active non-dividing chondrocytes. Since the chondrocytes are metabolically active, the chondrocytes would appear to produce a small amount of extracellular matrix macromolecules even though not dividing.

In line 23 of claim 83, the specification fails to disclose isolating chondrocytes from human donor's joint tissue. The specification discloses only implanting the construct in a joint cartilage lesion.

In lines 25-26 of claim 83, the specification fails to support or recite "collagen containing solution, gel or thermo-reversible hydorgel" as alternatives.

In lines 28-29 and 36 of claim 83, the specification fails to support or recite "sponge, scaffold, honeycomb or lattice" as alternatives.

In lines 31-34 of claim 83, the specification fails to support or recite "collagen containing glycosaminoglycan, agarose or hyaluronin" and "collagen containing proteoglycan, glycoprotein, gelatin, fibronectin, laminin, bioactive peptide, growth factor or cytokine".

In lines 45-46 of claim 83, the specification fails to support or recite "activation regimen repeated for from about one week to about three months".

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In line 1 of claim 83, "consisting essentially of" is uncertain as to meaning and scope. materials permitted and excluded by this limitation is uncertain.

In line 2, and where recited in any other line of claim 83, "comprising" is confusing since line 1 recites "consisting essentially of".

In line 2 of claim 83, "newly developed immature" is uncertain as to meaning and scope. Being "newly" and "immature" is relative and subjective.

In line 5 of claim 83, reciting "95:5%" is confusing since a ratio is normally not expressed as a percent. Also, does the percent also apply to "95"?

Claim 83 is confusing and unclear by being product-by-process by defining the claimed implantable construct in terms of process steps and conditions of how the construct is produced, and not setting forth clear, distinct and positive process steps in the order they are carried out such that there is a clear relationship between the steps, and each step has clear antecedent basis in a previous step. After the preamble, the claim contains only wherein clauses including process steps and conditions. Such wherein clauses do not set forth clear, distinct and positive process steps in a product-by-process claim. A product-by-process claim must set forth process steps as would be recited in a process of making the product. See MPEP 2113 and 2173.05(P) as to the proper form of a product-by-process claim.

In line 2, claim 64 is unclear by not having clear antecedent basis for "said collagenous support".

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

The claims are drawn to an implantable construct consisting essentially of a newly developed immature hyaline cartilage comprising a support matrix embedded with activated chondrocytes and an extracellular matrix produced by the activated chondrocytes wherein a ratio of extracellular matrix to chondrocytes is lower than 95:5% and wherein the chondrocytes are rejuvenated chondrocytes activated from inactive non-dividing chondrocytes to activated chondrocytes by repeatedly applying to inactive non-dividing chondrocytes embedded in the matrix a cyclic hydrostatic pressure followed by a constant atmospheric pressure wherein the activation results in cell proliferation, production of DNA, extracellular matrix macromolecules Type II collagen and S-GAG. The construct is prepared by isolating inactive chondrocytes from joint cartilage by subjecting the cartilage to enzymatic digestion, expanding the chondrocytes in a culture medium, suspending the expanded chondrocytes in a collagen solution, gel or thermo-reversible hydrogel, seeding the suspension in a support matrix which is a sponge, scaffold, honeycomb or honeycomb or lattice having pores 100 to 300 um in size. The seeded support is subjected to an activation, which comprises applying to the seeded support a cyclic hydrostatic pressure from about 0.01 to 10 MPa above atmospheric pressure at a frequency of from about

0.01 to 2 Hz for about one hour to 30 days followed by a resting period from about one day to sixty days, and the activation repeated for about one week to about three months. During activation, perfusion with a perfusion medium is performed at a flow rate from about 1 to 50 uL per minute. The formed construct comprises more than 5% of activated chondrocytes, and has a ratio of newly synthesized extracellular matrix to activated chondrocytes in the construct lower than 95:5.

Smith et al disclose repair and regeneration of cartilage by a process that involves *in vivo*, *ex vivo* or *in vitro* treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery *in situ* (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In* vitro treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

A cartilage construct produced by the process of Smith et al is the same the construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. The process of Smith et al will inherently produce a construct having at least 5% activated chondrocytes, and a ratio of newly synthesized extracellular matrix to activated chondrocytes lower than 95:5.

The presently claimed invention is not disclosed in parent application 10/104,677, and the parent application cannot be relied on for a priority date earlier than the filing date the present application.

***Response to Arguments***

The response urges that Smith et al do not suggest a construct consisting essentially of a newly developed immature hyaline cartilage construct comprising rejuvenated chondrocytes able to produce new extracellular matrix in a support matrix by the process claimed. However, Smith et al isolate chondrocytes that are inherently mature (Example 1) since they are adult articular chondrocytes from radiocarpal joints (col 16, lines 65-67). These chondrocytes are inherently non-dividing and inactive, and inherently result in hyaline cartilage being produced. The present specification discloses no source of cartilage for isolating chondrocytes other than disclosed by Smith et al. Applying hydrostatic pressure at a frequency disclosed by Smith et al inherently rejuvenates the isolated chondrocytes so the chondrocytes proliferate and produce DNA, extracellular matrix Type II collagen and S-GAG as evidenced by Smith et al disclosing (col 11, lines 7-10) that the hydrostatic pressure increases metabolic activity and decreases expression of destructive enzymes of chondrocytes.

The response points to process conditions of the present claims. However, there is inadequate evidence to support that any process conditions of the claims that may not be disclosed by Smith et al result in a construct materially different than results from the process of Smith et al.

***Claim Rejections - 35 USC § 103***

Claims 64-67, 69-71, 73-75 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg (6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al are described above.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by *in vitro* culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting. The resultant construct will be a cartilage construct as presently claimed, and will inherently have a ratio of newly synthesized extracellular matrix to activated chondrocytes of lower than 95:5. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. Suspending the

chondrocytes of Smith et al in a solution such as a collagen solution before seeding the cells in the matrix is suggested by Lee et al suspending cells in a solution such as collagen solution, before seeding, (col 6, line 21, and col 13, lines 11-26) that forms a second matrix component. The collagen solution would have been expected to gel and form a scaffold for the chondrocytes. The conditions of dependent claims are suggested by conditions used by the references. Lee et al suggest a sponge and Burg suggests temperature-dependent hydrogels as a matrix for seeding cells to implant. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen as in claim 70 would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 71 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

***Response to Arguments***

The response urges that Smith et al and the other references do not suggest process conditions of the present claims. However, for reasons set forth, conditions that are the same or substantially the same are suggested by Smith et al, and the suggested conditions will inherently provide results of perfusion, and oxygen and carbon dioxide concentration disclosed in the specification. Moreover, examples in the specification use a combination of conditions not required by the present claims, and other conditions within the scope of the claims may not produce results shown in the examples and Tables 3 and 4.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David M. Naff/
Primary Examiner, Art Unit 1657

DMN
6/24/08